



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : C08B 31/18, 15/02, C07C 51/285, C07H 7/033</p>	<p>A1</p>	<p>(11) International Publication Number: WO 99/57158 (43) International Publication Date: 11 November 1999 (11.11.99)</p>
<p>(21) International Application Number: PCT/NL99/00272 (22) International Filing Date: 4 May 1999 (04.05.99) (30) Priority Data: 98201495.3 7 May 1998 (07.05.98) EP (71) Applicant (for all designated States except US): NEDERLANDSE ORGANISATIE VOOR TOEGEPAST NATUURWETENSCHAPPELIJK ONDERZOEK TNO [NL/NL]; Schoemakerstraat 97, P.O. Box 6080, NL-2600 JA Delft (NL). (72) Inventors; and (75) Inventors/Applicants (for US only): VAN DER LUGT, Jan, Pieter [NL/NL]; Schone van Boskoopgaarde 15, NL-3824 AA Amersfoort (NL). JETTEN, Jan, Matthijs [NL/NL]; Costerlaan 3B, NL-3701 JL Zeist (NL). BESEMER, Arie, Cornelis [NL/NL]; Burg. H. v.d. Boschstraat 111, NL-3958 CC Amerongen (NL). VAN DOREN, Hendrik, Arend [NL/NL]; Schrijnwercklaan 15, NL-3828 XB Hoogland (NL). (74) Agent: DE BRUIJN, Leendert, C.; Nederlandsch Octrooibureau, Scheveningseweg 82, P.O. Box 29720, NL-2502 LS The Hague (NL).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>
<p>(54) Title: PROCESS FOR SELECTIVE OXIDATION OF PRIMARY ALCOHOLS (57) Abstract Primary alcohols, especially in carbohydrates, can be selectively oxidised to aldehydes and carboxylic acids in a low-halogen process by using a peracid in the presence of a catalytic amount of a di-tertiary-alkyl nitroxyl (TEMPO) and a catalytic amount of halide. The halide is preferably bromide and the process can be carried out at nearly neutral to moderately alkaline pH (5-11). The peracid can be produced or regenerated by means of hydrogen peroxide or oxygen. The process is advantageous for producing uronic acids and for introducing aldehyde groups which are suitable for crosslinking and derivatisation.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

Process for selective oxidation of primary alcohols

The invention relates to the selective oxidation of primary alcohols, using an oxidising agent in the presence of a catalytic amount of a di-tertiary-alkyl nitroxyl compound, especially 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO).

Such a process is known from *Tetrahedron Lett.* 34, 1181-1184 (1993), which describes the oxidation of monosaccharides wherein the non-primary hydroxyl groups are partly protected, using sodium hypochlorite, potassium bromide and TEMPO in a two-phase solvent system (dichloromethane and water) to produce the corresponding uronic acid. WO 95/07303 describes a process for oxidising carbohydrates with hypochlorite/TEMPO, using a pH of 9-13 in an aqueous medium. The oxidation of carboxymethyl and hydroxyethyl derivatives of starch and cellulose and other starch ethers with TEMPO is described in WO 96/38484.

These prior art oxidations have the advantage of being selective, in that oxidation of primary alcohol groups is strongly favoured over oxidation of secondary alcohol groups. However, the known processes use hypochlorite as the actual oxidising agent and thus produce chloride and some chlorinated byproducts: for complete oxidation of primary alcohols to carboxylic acids, two molar equivalents of hypochlorite are used and two molar equivalents of chloride are produced. This is serious drawback as there is an increasing need for low-chlorine or even chlorine-free oxidation processes.

It was found now that the oxidation of primary alcohol functions can be carried out without using equivalent amounts of chlorine compounds and with the possibility of using hydrogen peroxide as the ultimate oxidising agent. The process of the invention is defined by the characterising features of the appending claims.

In the following description, reference is made to TEMPO only for the sake of simplicity, but it should be understood that other di-tert-alkyl nitroxyls, such as 4,4-dimethyloxazolidine-N-oxyl (DOXYL), 2,2,5,5-tetramethylpyrrolidine-N-oxyl (PROXYL) and 4-hydroxy-TEMPO and derivatives thereof and those described in WO 95/07303 can be substituted for TEMPO. The catalytic amount of nitroxyl is preferably 0.1-2.5% by weight, based on the primary alcohol, or 0.1-2.5 mol% with respect to the primary alcohol.

The halide present in the process of the invention serves for regenerating TEMPO. The halide may be chloride, but preferably it is bromide. The halide may be

added to the reaction mixture as such, but it may also be added as an equivalent thereof or as molecular halogen. The halide ions are oxidised to molecular halogen by the peracid, and the molecular halogen regenerates TEMPO. Thus, both TEMPO and the halide need to be present in a catalytic amount only. The catalytic amount of halide may be 0.1-40, preferably from 0.5 to 10 mol%, with respect to the primary alcohol.

The peracid may be any peralkanoic acid such as peracetic acid, perpropionic acid, perlauric acid etc., a substituted alkanoic acid such as peroxytrifluoroacetic acid, an optionally substituted aromatic peracid such as perbenzoic acid or m-chloroperbenzoic acid, or an inorganic peracid such as persulphuric acid or salts of any of the above peracids, e.g. potassium peroxymonosulphate, commercially available under the name Oxone ®. The peracids may be formed in situ from a precursor such as the corresponding aldehyde, (carboxylic) acid, acid anhydride, ester or amide, e.g. tetra-acetyl-ethylenediamine, with a suitable halogen-free oxidising agent, such as hydrogen peroxide or oxygen, either before the oxidation reaction or during the oxidation reaction.

The process of the invention results in oxidation of primary alcohols initially to the corresponding aldehydes, and eventually to the corresponding carboxylic acids. In general, the second oxidation step, from aldehyde to carboxylic acid, proceeds at a faster rate than the first step, i.e. the oxidation from alcohol to aldehyde. Under usual experimental conditions, the maximum fraction of aldehyde functions present will be between about 10 and 15% (based on the number of primary hydroxyls available for oxidation). The present process is especially favourable for the selective oxidation of primary hydroxyl groups in alcohols having a secondary alcohol function in addition to the primary alcohol, such as 1,6-octanediol, 1,9-octadecanediol, sugar alcohols, glycosides, and in particular carbohydrates having primary alcohol functions such as glucans (starch, cellulose), furanofructans, galactans, (galacto)mannans, and the like. A particular group of compounds suitable for oxidation with the present process are hydroxyalkylated, especially hydroxyethylated carbohydrates such as hydroxyethyl starch or hydroxyethyl inulin. These derivatives result in an alternative way for producing formylmethyl and carboxymethyl carbohydrates.

The oxidation of carbohydrates containing primary hydroxyl groups results in the corresponding carbohydrates containing aldehydes and/or carboxylic acids with intact ring systems. Examples include α -1,4-glucan-6-aldehydes, β -2,1-fructan-6-aldehydes and β -2,6-fructan-1-aldehydes, with the corresponding carboxylic acids. Where these products

still contain the aldehydes, they are useful intermediates for functional carbohydrates wherein the aldehyde groups are further reacted with e.g. amine compounds and the like. They are also useful intermediates for crosslinked carbohydrates, in which the aldehyde groups are further reacted with e.g. diamine reagents.

5

Example 1: Oxidation of methyl α -D-glucopyranoside (MGP)

One gram of MGP (5.15 mmol) was dissolved in 60 ml of water at room temperature. To this solution were added 200 mg NaBr (1.94 mmol), 20 mg TEMPO (0.13 mmol), 10 mg EDTA (for stabilising the oxidising agent) and 2.5 g NaHCO₃. Peracetic acid (1.32 mmol/ml) was added at a rate of 200 μ l per 10 minutes until an excess amount, calculated on a theoretical basis for 100% oxidation to 6-carboxylic acid (14.6 mmol), had been added. The pH was maintained at 7 by addition of 1 M NaOH using a pH-stat. The reaction time was 8 hr. The degree of oxidation, determined using the Blumenkrantz method with galacturonic acid as a reference, was 95%. High Performance Anion Exchange Chromatography (HPAEC) shows that the degree of oxidation is greater than 95%. No other peaks than the uronic acid and a trace of starting material were detected.

Example 2: Oxidation of α -D-glucopyranosyl phosphate (α -Glc-1-P)

1.97 g of α -Glc-1-P ($2K^+ \cdot C_6H_{11}O_9P^{2-} \cdot 2H_2O$, 5.5 mmol) was dissolved in 60 ml of water at room temperature. To this solution was added 210 mg KBr (1.76 mmol), 20 mg TEMPO (0.13 mmol), 10 mg EDTA, and 2.5 g KHCO₃. Peracetic acid (10 ml, 1.69 mmol/ml) was added at a rate of 200 μ l per 10 minutes. The pH was maintained at 8 by addition of 2M KOH using a pH-stat. After 16 h the reaction was complete. The product crystallized from the mixture after addition of MeOH to obtain α -D-glucopyranuronic acid 1-phosphate ($3K^+ \cdot C_6H_8O_{10}P^{3-} \cdot 5H_2O$, 1.90 g, 4.0 mmol, 73%). NMR (500 Mhz, D₂O, in ppm): ¹H δ 3.32 (dd, H-4, J_{3,4} = 9.5 Hz, J_{4,5} = 9.9 Hz), 3.35 (m, H-2, J_{P,12} = 1.8 Hz, J_{1,2} = 3.4 Hz, J_{2,3} = 9.5 Hz), 3.62 (dd, H-3, J_{2,3} = 9.5 Hz, J_{3,4} = 9.5 Hz), 3.99 (d, H-5, J_{4,5} = 9.9 Hz), 5.30 (dd, H-1, J_{P,11} = 7.3 Hz, J_{1,2} = 3.4 Hz), ¹³C δ 71.4 (C-2), 71.5 (C-3,C-4), 72.4 (C-5), 93.0 (C-1), 176.6 (C-6).

30

Example 3: Oxidation of D-glucuronic acid

1.94 g of D-glucuronic acid (10 mmol) was dissolved in 50 ml water at room temperature. To this solution was added 196 mg KBr (1.65 mmol), 30 mg TEMPO (0.20 mmol), 10 mg EDTA, and 1.0 g KHCO_3 . Peracetic acid (8 ml, 1.69 mmol/ml) was added at a rate of 200 μl per 10 minutes. The pH was maintained at 8 by addition of 2M KOH using a pH-stat. After 16 h the reaction was complete. The reaction mixture was acidified with conc. HCl to pH = 3.4 and the product was crystallized to obtain D-glucaric acid, mono potassium salt ($\text{K}^+ \cdot \text{C}_6\text{H}_9\text{O}_8 \cdot \text{H}_2\text{O}$, 1.55 g, 0.62 mmol, 62%).

FT-IR (in cm^{-1}): 3379 (s), 3261 (s), 2940 (m), 1738 (s), 1453 (m), 1407 (m), 1385 (m), 1342 (m), 1267 (m), 1215 (m), 1108 (s), 1050 (m), 862 (m), 657 (m).

Example 4: Oxidation of starch at pH 5

1 gram of potato starch (6.17 mmol) was gelatinized in 60 ml water at 100°C. To this solution were added 200 mg NaBr (1.94 mmol), 20 mg TEMPO (0.13 mmol), 10 mg EDTA and 2.5 g sodium acetate at room temperature. Peracetic acid (1.51 mmol/ml) was added at a rate of 200 μl per 10 minutes until an excess amount, calculated on a theoretical basis for 100% oxidation to 6-carboxylic acid (13.6 mmol) had been added. The pH was maintained at 5 with 1.0 M NaOH using a pH-stat. The reaction time was 8 hours. The degree of oxidation (Blumenkrantz - polygalacturonic acid) was 26% 6-carboxyl starch.

Example 5: Oxidation of starch at pH 6

1 gram of potato starch (6.17 mmol) was gelatinized in 60 ml water at 100°C. To this solution were added 200 mg NaBr (1.94 mmol), 20 mg TEMPO (0.13 mmol), 10 mg EDTA, 1.25 g NaH_2PO_4 and 1.25 g Na_2HPO_4 at room temperature. Peracetic acid (1.30 mmol/ml) was added at a rate of 200 μl per 10 minutes until an excess amount, calculated on a theoretical basis for 100% oxidation to 6-carboxylic acid (13.8 mmol), had been added. The pH was maintained at 6 with 1.0 M NaOH using a pH-stat. The reaction time was 8 hours. The degree of oxidation (Blumenkrantz - polygalacturonic acid) was 40% 6-carboxyl starch.

Example 6: Oxidation of starch at pH 7

1 gram of potato starch (6.17 mmol) was gelatinized in 60 ml water at 100°C. To this

solution were added 200 mg NaBr (1.94 mmol), 20 mg TEMPO (0.13 mmol), 10 mg EDTA and 2.5 g NaHCO₃. Peracetic acid (1.35 mmol/ml) was added at a rate of 200 µl per 10 minutes until an excess amount, calculated on a theoretical basis for 100% oxidation to 6-carboxylic acid (18.4 mmol), had been added. The pH was maintained at 7 with 1.0 M NaOH using a pH-stat. The reaction time was 11.5 hr. The degree of oxidation, determined using the Blumenkrantz method with polygalacturonic acid as a reference, was 95% 6-carboxyl starch. The degree of oxidation, determined with HPAEC was 86% 6-carboxyl starch.

10 **Example 7: Oxidation of starch at pH 8**

Example 6 was repeated, however maintaining the reaction pH at 8. The consumption of peracetic acid was 13.9 mmol. The degree of oxidation (Blumenkrantz - polygalacturonic acid) was 91 % 6-carboxyl starch.

15 **Example 8: Oxidation of starch at pH 9**

Example 6 was repeated, however maintaining the reaction pH at 9. The consumption of peracetic acid was 11.9 mmol. The degree of oxidation (Blumenkrantz - polygalacturonic acid) was 90 % 6-carboxyl starch.

20 **Example 9: Oxidation of starch at pH 10**

Example 6 was repeated (using 2.5 g of Na₂HPO₄ instead of NaHCO₃). The consumption of peracetic acid (1.42 mmol/ml) was 14.3 mmol. The degree of oxidation was 37% 6-carboxyl starch.

Claims

1. A process for oxidising a primary alcohol using an oxidising agent in the presence of a catalytic amount of a di-tertiary-alkyl nitroxyl, *characterised* in that the alcohol is oxidised using a peracid or a salt or precursor thereof in the presence of a catalytic amount of halide.
2. A process according to Claim 1, wherein the halide is bromide.
3. A process according to Claim 1 or 2, wherein the di-tertiary-alkyl nitroxyl is 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO).
4. A process according to any one of Claims 1-3, wherein a pH of 5-11, especially 7-10 is used.
5. A process according to any one of Claims 1-4, wherein the peracid is a peralkanoic acid, especially peracetic acid.
6. A process according to any one of Claims 1-5, wherein the peracid is produced in situ from hydrogen peroxide.
7. A process according to any one of Claims 1-6, wherein the primary alcohol is a carbohydrate.
8. A process according to any one of Claims 1-6, wherein the primary alcohol is a hydroxyalkylated carbohydrate.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/NL 99/00272

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C08B31/18 C08B15/02 C07C51/285 C07H7/033

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C08B C07C C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 362 868 A (EUL ET AL.) 8 November 1994 (1994-11-08) example 9	1-8
Y	J. EINHORN ET AL.: "Efficient and highly selective oxidation of primary alcohols to aldehydes by N-chlorosuccinimide mediated by oxoammonium salts." J. ORG. CHEM., vol. 61, 1996, pages 7452-7454, XP000627291 page 7452	1-8

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

26 July 1999

Date of mailing of the international search report

05/08/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Lensen, H

INTERNATIONAL SEARCH REPORT

International Application No

PCT/NL 99/00272

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	A.E.J. DE NOOY ET AL.: "Highly selective tempo mediated oxidation of primary alcohol groups in polysaccharides." RECEUIL DES TRAVAUX CHIMIQUES DES PAYS-BAS, vol. 113, 3 March 1994 (1994-03-03), pages 165-166, XP000560836 page 165	1-8
A	US 5 334 756 A (PARFAIT J.M. LIKIBI ET AL.) 2 August 1994 (1994-08-02) column 7, line 8 - column 8, line 34	
A	US 5 739 352 A (BRUCE ARMIN BARNER ET AL.) 14 April 1998 (1998-04-14)	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/NL 99/00272

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5362868 A	08-11-1994	BR 9402469 A	24-01-1995
		CA 2126126 A	19-12-1994
		EP 0630906 A	28-12-1994
		FI 942939 A	19-12-1994
US 5334756 A	02-08-1994	BE 1006771 A	06-12-1994
		CH 683525 A	31-03-1994
		DE 4209869 A	01-10-1992
		FR 2674528 A	02-10-1992
		GB 2257149 A, B	06-01-1993
		GB 2281074 A, B	22-02-1995
		IT 1254313 B	14-09-1995
		JP 5194334 A	03-08-1993
		NL 9200556 A	16-10-1992
		US 5504246 A	02-04-1996
		US 5670685 A	23-09-1997
		US 5668261 A	16-09-1997
US 5739352 A	14-04-1998	NONE	

THIS PAGE BLANK (USPTO)